

AUREOMYCIN

A Review of the Clinical Literature

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Lederle

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Increasing clinical interest in aureomycin, which began almost two years ago with the description by Duggar¹ of its discovery and properties, has now provided a sufficient number of reports on its use to permit recapitulation and evaluation. The purpose here is to present a concise picture of the therapeutic action of aureomycin from the standpoint of clinical medicine, only a cursory glance being given to the results of bacteriologic, pharmacologic and other laboratory studies

ANTIBIOTIC ACTIVITY

The almost uniformly favorable tenor of the nearly 300 articles* already published is remarkable and the range of therapeutic indications extensive, with few other than minor drawbacks reported. They confirm the potency and unequalled versatility of this antibiotic.

Experimentally, aureomycin has been found to act *in vitro* as a bacteriostat and, at higher concentrations, as a bactericide, against a wide variety of pathogens, including salmonella, escherichia, neisseria, brucella, staphylococcus, streptococcus, and rickettsia, *Kl pneumoniae*, *Pr vulgaris*, *Sar lutea*, *Sar marcescens*, *B subtilis*, *B megatherium*, *A. aerogenes*, *H influenzae*, *Dipl pneumoniae*, *Ps aeruginosa* and the agents responsible for psittacosis and lymphogranuloma venereum ²⁻⁶

As compared with other antibiotics, such as penicillin and streptomycin, aureomycin shows little tendency to permit the development of drug-resistant strains. An important exception is *Pr vulgaris*, which tends to become highly resistant, a point of considerable importance in the treatment of urinary infections ³

The protective power of aureomycin against infections induced by the above organisms in experimental animals has been studied^{2,3,7-10} and found to agree in general with *in vitro* results.

Infections in man, produced by the organisms listed, respond, in the main, to aureomycin. Typhoid has not been found to give a clear-cut clinical response to the

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antibiotic There is some indication that a combination of aureomycin and penicillin which act synergistically in *S typhosa* infections in mice,¹¹ might give improved results against typhoid in man. Aureomycin is not effective against tuberculosis.

It is of practical therapeutic importance that a number of organisms which are, or have become, resistant to streptomycin or to penicillin are sensitive to aureomycin.

Dowling¹² and Long¹³ have published tabulations of the relative usefulness of aureomycin compared with other chemotherapeutic agents.

Herrell¹⁴ considers that since aureomycin appears to inhibit the causative agents of most of the common pneumonias, it is probably indicated in pneumonia, regardless of the etiology, and should almost always be used if bacteriologic facilities are not available.

PHARMACOLOGY

Whether given orally or by other routes, including the rectal,¹⁵ aureomycin readily passes into the bloodstream, maintaining measurable serum levels for as long as 12 hours¹⁶ after oral or intramuscular administration, and thence passes into the spinal fluid, peritoneal fluid,¹⁵ pleural fluid, bile, urine and milk,^{17,18} thus indicating wide diffusion throughout all the body tissues. It has been found in the liver, kidney, lung and spleen and can probably diffuse through the placenta to enter the fetal circulation.¹⁸ Doses of 5 to 10 mg per kilo of aureomycin,

given orally at 6-hour intervals, ensure the persistence of measurable blood levels.¹⁷ The drug appears rapidly and in high concentration in the urine,¹⁷ and can be detected for as long as 55 hours after a single oral dose of 0.5 or 0.75 Gm.⁸

Substantial amounts remain in the blood 2 hours after intravenous injection.¹⁹ The routine determination of serum levels is not recommended by Long,¹⁸ who considers that twice-daily observation of the patient will indicate the adequacy of treatment. When an infection, known to be curable by aureomycin, exhibits continuing fever, the dosage should be increased.

The toxicity of aureomycin is very low.^{3, 8, 19-22} Occasionally, some degree of nausea, vomiting or diarrhea has been noted, particularly in ambulant patients, although it has rarely been necessary to discontinue the drug on this account. Improved production methods have reduced this effect to very minor importance. Hill and associates²³ have noted that, in over 100 cases of various infections, side reactions were mild.

Aureomycin causes some tissue irritation²⁴ so that intramuscular injection is not recommended. In a concentration of 0.5 per cent, aureomycin borate does not irritate the conjunctiva.²⁵

Hill's group²³ and Sanders and his colleagues²⁶ observed a number of cases of phlebitis among patients treated intravenously with aureomycin, but it usually subsided quickly without residual effects. The present glycine diluent is believed to lessen the likelihood of such occurrences.

It is to be anticipated that as the number of patients treated by aureomycin increases, there will be found some who will develop a more serious reaction, particularly in the allergic type of patient and in conditions with a tendency toward the development of Herxheimer reactions. A few such cases have been reported ^{27,28}

When aureomycin, or any other oral antibacterial agent, is given over extended periods, the possibility of interference with the intestinal synthesis of vitamins suggests the advisability of giving vitamin supplements, especially vitamin B complex

CLINICAL USAGE

Coccal Infections

Gram-Positive Cocci

Staphylococcus — The staphylococcus exhibits an innate tendency to produce localized collections of pus. As a rule, these occur in the skin and other surface tissues, where they are readily accessible to treatment. If the organisms break through the cell barrier to produce bacteremia, a grave condition is the result. Abscess may then occur anywhere in the body, unless the septicemia is so overwhelming that death occurs within 2 or 3 days.

Prior to the advent of aureomycin, penicillin was pre-eminent for the treatment of staphylococcal infections and is still of some importance.

SEPTICEMIA—An increasing number of infections are appearing which are produced by strains resistant to penicillin but sensitive to aureomycin²⁹

Nichols and Needham³⁰ administered aureomycin to 6 patients with penicillin-refractory staphylococcic bacteremia, with recovery in 4 and temporary improvement in 2. Previous therapy with streptomycin in 4 cases and with sulfonamides in 3 had been unsuccessful. Spink and Yow³¹ obtained recovery in 4 of 5 similar cases; 1 patient with agranulocytosis died.

Ross and co-workers³² reported negative blood culture and normal temperature 12 hours after beginning aureomycin-sulfadiazine therapy, in a child critically ill with *Staphylococcus aureus* septicemia and not responding to massive doses of penicillin and streptomycin. Long, Schoenbach and their colleagues³³ obtained gratifying results in 2 additional cases of *Staphylococcus aureus hemolyticus* bacteremia. In 3 cases of *Staphylococcus aureus* bacteremia, treated by Dowling and co-workers,³⁴ equally good results were observed. Blood cultures were sterile within 24 hours, and temperatures returned to normal within a few days. Penicillin had been ineffective in 2 of these.

MENINGITIS—Subarachnoid hemorrhage complicating sickle-cell anemia is one of the rarest of conditions, only 9 cases appearing in the medical literature. Almklov and Hansen³⁵ have successfully used aureomycin in the treatment of one case of *Staphylococcus albus* meningitis, arising as a sequel to this complication in a child with sickle-cell anemia. Schoenbach³⁶ has reported the cure with aureomycin of a case of postoperative meningitis secondary to

drainage of a *Staphylococcus aureus* brain abscess and a case reported by Nichols and Needham³⁰ also recovered Reilly³⁷ considers aureomycin the most satisfactory remedy for staphylococcal meningitis.

PULMONARY INVOLVEMENT—Schwachman and co-workers³⁸ used aureomycin in 35 cases of pulmonary involvement associated with pancreatic fibrosis. In all cases, *Staphylococcus aureus* was isolated from the nasopharynx. The response was excellent in 24 cases, good in 5, and fair in 2, with no change in 4. Many of these children, who ranged in age from 5 weeks to 12 years, had been given dietary treatment for years. In 31 cases, improvement began within 2 or 3 days and included disappearance of cough, diminution of fever and marked increase in weight (even in the presence of diarrhea), appetite and sense of well-being. Continuous administration is requisite to prevent relapse and no untoward effect has been demonstrated with continuous therapy for more than 4 months.

PNEUMONIA—Staphylococcic pneumonia has been successfully treated with aureomycin by Olshaker and co-workers³⁹ and by Collins.⁴⁰ Long and associates,³³ reporting the favorable results of aureomycin therapy in 8 patients with *Staphylococcus aureus hemolyticus* infections of varied type, in several of whom sulfadiazine and penicillin had been ineffective, have mentioned the rapid recovery of one case of pneumonia which had been refractory to penicillin.

PULMONARY ABSCESS—Harvey and associates⁴¹ obtained dramatic improvement following aureomycin therapy in

an acute case of multiple staphylococcic abscess of the lung, although penicillin had apparently been ineffective

SINUSITIS—In 9 acute and 9 chronic sinus infections, reported by Peterson and Hadley,⁴² the invading organisms included *Staphylococcus aureus* and *albus*. These infections cleared rapidly following the use of oral aureomycin. Remarkable improvement, or complete recovery, took place in the chronic cases, several of which had previously been subjected to intensive medical and surgical treatment without effect, and all the acute cases appeared to be completely cured.

OTITIS MEDIA—Although otitis media frequently responds to penicillin, Thumm⁴³ has reported a resistant case of *Staphylococcus aureus hemolyticus* otitis in an adolescent girl. No improvement had followed 2 weeks of penicillin, but there was resolution after 3 days of aureomycin. The canal was dry in 48 hours.

Whitlock⁴⁴ treated with aureomycin a case of purulent draining otitis media of 2 months' duration, in a three-month-old infant. Staphylococci were cultured from one ear and *E. coli* from the other. Administration of 50 mg of aureomycin every 6 hours stopped the discharge and healed the inflammation within 12 days. The child was discharged 2 days after treatment was stopped. There had been no recurrence 1 month later.

SKIN INFECTIONS AND BREAST ABSCESS—The oral administration of aureomycin has been found to produce rapid clearing of skin and breast abscess produced by staphylococci.^{20,45}

Leven⁴⁶ obtained cure with aureomycin in an appar-

ently hopeless case of extensive and badly infected burns in a child who also developed pyemia and osteomyelitis of the mandible and who was sensitive to sulfonamide and penicillin. Prompt improvement followed, with return to normal temperature, and it was very soon possible to do skin grafting.

The local use of aureomycin has been found, by Hollander and Hardy⁴⁷ to be highly satisfactory as a surgical dressing and in the treatment of pustular dermatosis. In a few of the latter cases, local sensitivity was noted. No reactions were observed when the ointment was used as a surgical dressing, a fact which may indicate its usual behavior on normal skin.

Breast abscess contracted by nursing mothers from their babies created a problem recently in a Canadian hospital.⁴⁸ It was found that the administration of aureomycin to the infants, (who harbored *Staphylococcus aureus hemolyticus* in the nasopharynx) not only prevented the formation of skin pustules in the babies but proved to be the best method of controlling the epidemic. If the mother received aureomycin within the first 48 hours after the appearance of breast symptoms, abscess formation could usually be prevented. Occasionally surgical drainage was required, but the tissues then healed rapidly.

OCULAR INFECTIONS—Kennedy⁴⁹ found aureomycin solution effective when used topically for external ocular infections. In 23 mild cases of *Staphylococcus aureus* conjunctivitis and in 74 severe cases, Braley and Sanders⁵⁰ obtained clinical cure in a total of 95 with one failure in each group. They used a 0.5 per cent solution of aureo

mycin borate in isotonic sodium chloride solution (pH 7.5 to 7.8). Favorable results have been noted in cases of ocular infections treated on the ophthalmic service of Boston City Hospital.⁵⁰

BONE AND JOINT INFECTIONS—Wright and Schreiber⁵¹ have mentioned that the use of aureomycin in compound fractures has resulted in a lower incidence of osteomyelitis. The antibiotic has also been found effective in established cases of osteomyelitis.⁵²

Streptococcus—The types of infection produced by the hemolytic (beta) and the nonhemolytic (alpha and gamma) streptococci exhibit a number of points of difference. Nonhemolytic streptococci rarely of themselves cause infection in man, but in conditions of lowered local or general resistance they may invade damaged tissue. They are thus frequently found as secondary invaders of an infected area or as the cause of subacute bacterial endocarditis. Hemolytic streptococci are those most frequently responsible for human infections. They are highly invasive, produce early toxemia, and require but a short incubation period before overwhelming the defenses of the host.

The sulfonamides were the first drugs to produce a therapeutic effect in streptococcal infections. Later, they were partially superseded by penicillin, but they still remain an alternative choice and supplementary resource. Recently, aureomycin has been found highly effective and it is generally considered equal or superior to penicillin in beta-hemolytic infections. In combating disease caused

by nonhemolytic streptococci, it is not as yet possible to name the best antibacterial agent for controlling these organisms

PNEUMONIA—Aureomycin has proved to be highly effective in streptococcal pneumonia ^{40,53-55} Olshaker and Ross³⁹ have also reported striking clinical and bacteriological response in child patients. Resolution of the pneumonic process was rapid in most cases, and the drug was well tolerated when given by mouth. Normal temperatures and marked clinical improvement resulted in almost every case after 12 to 36 hours of treatment, and were accompanied by X-ray evidence of rapid resolution.

ERYSIPELAS—Brainerd and co-workers⁴⁵ have reported satisfactory response to aureomycin in 1 patient with erysipelas.

CELLULITIS—A case of streptococcal cellulitis (beta-hemolytic) recovered within 24 hours on aureomycin therapy ³⁴

SCARLET FEVER—Dowling and co-workers³⁴ have obtained good results with aureomycin in 9 cases of scarlet fever. The temperature promptly fell in every case and there were no complications.

TONSILLITIS—One case of streptococcal tonsillitis has been reported as responding well to aureomycin ⁴¹ Three of the influenza cases (p 46) successfully treated with aureomycin by Finland and his colleagues⁵³ had a concomitant nasopharyngitis and tonsillitis associated with beta-hemolytic streptococci. Aureomycin may prove valuable in preparing cardiac patients for tonsillectomy who must be guarded against even transient bacteremia.

RHEUMATIC FEVER — Herrell¹⁴ advocates the use of aureomycin prophylactically for the prevention of recurrences of rheumatic fever, and believes that it may supplant penicillin for this purpose

ENDOCARDITIS—In a case of endocarditis,³⁴ with blood cultures positive for alpha- and beta-hemolytic streptococci, and further complicated by heroin addiction, uneventful recovery followed the oral use of aureomycin for 8 weeks. After an initial dose of 1.5 Gm, the drug was given in a dosage of 750 mg every 6 hours. Long, Schoenbach and co-workers³³ have reported apparent cure in 2 cases of subacute bacterial endocarditis due to *Streptococcus faecalis*. Harvey and Mirick⁴¹ obtained equally good results in another case with this type of infection and improvement in 3 others, 1 with *Streptococcus faecalis* invasion, 2 with a microaerophilic streptococcus.

Herrell¹⁴ recommends the prophylactic use of aureomycin, pre- and post-operatively, in all patients with organic heart disease. In view of the danger of bacteremia, and consequent subacute bacterial endocarditis in such cases, he believes that at least 1 or 2 days of antibiotic preparation are essential before operating on any part of the alimentary or genitourinary systems.

MENINGITIS—One patient with *Streptococcus faecalis* meningitis has been reported by Long and his co-workers³³ as having been rapidly cured by aureomycin.

BACTEREMIA—A case of bacteremia caused by beta-hemolytic streptococci responded readily to aureomycin.³⁴

SINUSITIS—In the 18 cases of sinusitis discussed under the heading of staphylococcal infections,⁴² hemolytic strep-

tococci were also present and responded as rapidly as did the staphylococci

OCULAR INFECTIONS—Braley and Sanders⁵⁵ believe that aureomycin will prove of distinct value in streptococcal infections of the eye, although they have not reported treating any such cases. They recommend combined local and systemic therapy.

PUERPERAL SEPSIS—Recent unpublished work suggests that aureomycin is indicated for the prevention of puerperal sepsis. The blood and bacterial spectrum of aureomycin gives maximum protection to the patient and extends optimal freedom to the obstetrician in any surgical procedures undertaken.

PERITONITIS—Wright and co-workers⁵⁶ have reported that a number of cases of acute appendiceal peritonitis, in which various strains of streptococcus appeared to be the sole invaders, have responded well to aureomycin. The offending organism was beta-hemolytic streptococcus in 2 cases, *Streptococcus viridans* and gamma streptococcus in 1 case, *Streptococcus viridans* alone in 2 cases, gamma streptococcus alone in 1 case, anerobic streptococcus in 4 cases, 3 of which were fatal. Yeager and co-workers⁵⁷ successfully treated a case of a peritonitis (caused by beta-hemolytic streptococcus) in a four-year-old child, following rupture of the appendix.

Pneumococcus—The pneumococcus is comparatively sensitive to chemotherapeutic agents. The sulfonamides give good results, but those with penicillin are better. Aureomycin is now considered the drug of choice in pneumonia.

because of its very wide antibacterial spectrum and its effectiveness against primary atypical pneumonia

PNEUMONIA—In pneumococcal pneumonia, the results of aureomycin therapy are comparable to those of penicillin^{21 40} Among 43 cases (7 with bacteremia) reported by Dowling and co-workers,³⁴ there were 3 deaths, 2 of them shortly after commencing therapy In most of the survivors, normal temperatures were reached within 24 to 48 hours Similar results were noted by a number of other authors^{17 39,41 53}

Of a series of 33 cases reported by Gocke and co-workers,⁵⁹ 11 with bacteremia, and 1 with suspected pleural effusion, aureomycin brought about recovery in all but 2 cases Four cases treated by Collins and associates⁵⁸ recovered

Recently, Kenig⁶⁰ has reported a case of lobar pneumonia in an obese alcoholic patient, which showed no improvement with combined penicillin and sulfadiazine during 10 days of treatment The temperature (103° F) was slightly higher at the end of this period There was immediate response to aureomycin on its substitution for the previous medication The temperature was normal 3 hours after the initial dose (500 mg), marked clinical improvement was evidenced by the next day, and the lungs were clear on the sixth day of treatment.

MENINGITIS—Aureomycin was apparently responsible for prompt recovery in a sixty-two-year-old patient with pneumococcal meningitis³⁴ and in a case each of Type 6,³³ Type 19,⁴¹ and Type 29¹⁷ meningitis The patient with Type 6 meningitis had been treated with sulfadiazine and

penicillin but the organism had developed resistance to both, and the spinal fluid was very definitely infected. Recovery was prompt following institution of aureomycin therapy. Oral administration of aureomycin was apparently adequate for the speedy control of the infection in all these cases.

Dowling and co-workers⁶¹ have reported a case, of unspecified type, which recovered on aureomycin alone.

OCULAR INFECTIONS—Clinical cure, without recurrence, followed the use of aureomycin every hour for 16 hours, in 5 cases of pneumococcal conjunctivitis.^{25 62} The antibiotic was used locally in the form of a 0.5 per cent solution of aureomycin borate in isotonic saline.

Gram-Negative Cocci

Neisseria Meningitidis (Meningococcus)—The meningococcus may be found in the pharynx of normal persons especially during an epidemic. Increase in the numbers of bacteria present, or in their virulence, or lowered tissue resistance, may permit entry of the organisms into the blood stream. Such a bacteremia is probably always an antecedent to the development of meningitis and the recognition and treatment of the infection during this early stage would greatly improve the outlook for the patient. This is, of course, infrequently possible. The organism is readily attacked by the sulfonamides or by penicillin, and the following reports indicate that aureomycin is also effective.

BACTEREMIA—Shaw⁶³ has reported a case of meningococcemia in a child, which clinically resembled rickettsial

disease Acting on this presumptive diagnosis, he administered aureomycin Two hours later, the patient was greatly improved However, the petechial eruption had become so characteristically meningococcic that sulfadiazine was then given The patient was almost entirely well the next morning and Shaw⁶³ believes that aureomycin was the actual curative agent Bacteriologic studies showed meningococcemia with normal spinal fluid Finland and co-workers^{21 54} have observed a very similar case The patient became afebrile after the first dose, clinical improvement was noticeable within 18 hours, and there were no further positive blood cultures

Neisseria Gonorrhoeae (Gonococcus)—Although the gonococcus primarily causes disease of the genitourinary tract, it may attack mucous and serous surfaces elsewhere Bacteremia is much rarer than in meningococcal infections Penicillin is at present the accepted drug for gonorrhea Suitable early treatment is highly desirable to prevent the formation of local urinary foci, or bacteremia with possible invasion of the joints or cardiac valves

URETHRITIS AND CERVICITIS—Good results were obtained by Collins and associates⁶⁴ in 148 male patients with acute gonorrheal urethritis Various oral dosage schedules were used, the total varying from 1.0 to 3.5 Gm given over periods of $\frac{1}{2}$ to $2\frac{1}{2}$ days The cure rate was apparently lower than with penicillin; but the estimate of cure was based on an examination on the day following therapy and in view of the prolonged urinary excretion of aureomycin, it seemed likely that a later

examination would have found a higher recovery rate. Follow-up showed 87 per cent cured, about half of the "failures" appeared to be re-infections.

Robinson⁶⁵ has reported a cure rate of 70 per cent in a group of 70 patients given 1.0 Gm. of aureomycin in a single dose and notes that 3 of the failures later failed to respond to 75,000 units of procaine penicillin. He considers that the drinking of alcoholic beverages definitely interferes with the action of antibiotics in this type of infection.

Aureomycin should be of great value in the treatment of penicillin-resistant cases, but it is open to the same objection as is penicillin with regard to its possible "masking" effect on a syphilitic lesion.^{66 67} Patients should always be given serological follow-up for possible lues.

Chen, Dienst, and Greenblatt⁶⁸ obtained 100 per cent cure in 20 cases (male and female), given 1.0 Gm. aureomycin thrice daily after meals, for 2 days. Two cases had been unsuccessfully treated with penicillin. Another male patient, not in the above group, who had received more than 6,000,000 units of penicillin over a period of about 4 months, was apparently cured by the above dose of aureomycin. The urethral discharge disappeared permanently after the first dose. Two cases of gonococcal urethritis treated with aureomycin were reported cured by Willcox and Findlay.⁶⁹

EPIDIDYMITIS—One of the 148 cases of urethritis⁶⁴ reported above had a severe epididymitis which promptly subsided following therapy.

Bacillary Infections

Gram-Positive Bacilli

Corynebacterium — Hitherto, chemotherapeutic agents have been of little value in attacking the corynebacteria and have no effect on the toxins produced by these organisms. In a case of corynebacterium peritonitis of 6 months' duration, the use of aureomycin is believed by Rhoads⁷⁰ to have been the turning point in the illness, which then proceeded to recovery

Bacillus Anthracis—Anthrax is a rare condition in this country. Penicillin has hitherto been the remedy of choice, with or without sulfadiazine, but Ruiz-Sánchez and associates⁷¹ have reported 2 cases of anthrax carbuncles in man which responded very favorably to aureomycin, with rapid local and general improvement and disappearance of fever within 3 days

A clinically and culturally diagnosed case of anthrax in a wool-carder employed in a Pennsylvania mill, reported by Gold,⁷² was treated in the office with oral aureomycin, 750 mg every 4 hours. During the first 24 hours, no change was noted except for a considerable extension of the edema surrounding the initial lesion on the wrist, but 48 hours after beginning treatment, very little swelling remained. On the fourth day of therapy, the eschar was dry and free of anthrax bacilli, and there was neither edema nor adenopathy. The patient returned to work after a disability period of 14 days.

A second case, an employee of the same mill, re-

sponded similarly. The clinical results in these patients compare favorably with those produced by penicillin, although bacteriologic cure seems to be slower. The extension of edema occurring in both these patients early in the course of treatment has been observed also with penicillin.

Clostridium—Yeager and co-workers⁵⁷ successfully used aureomycin together with appendectomy and drainage in a case of *Clostridium welchii* peritonitis, secondary to appendiceal perforation.

Moraxella Lacunata (Diplobacillus of Morax-Axenfeld)—OCULAR INFECTIONS—Four out of 5 patients with *Moraxella lacunata* conjunctivitis were clinically cured by the local use of aureomycin.²⁵ The fifth patient suffered a relapse after treatment had been discontinued. Aureomycin seems to be the best weapon against this organism, which has not previously yielded satisfactorily to any type of treatment.

Gram-Negative Bacilli

Escherichia—The *Escherichiae* and related bacteria, when they develop pathogenicity, are most frequently found in the genitourinary tract and will be further discussed in the section on "Mixed Infections." They commonly cause peritonitis or wound infection, and occasionally cause pneumonia or meningitis. The sulfonamides and streptomycin have been used with a certain degree of success, but aureomycin seems to provide the most effective form of therapy.

BACTEREMIA—Collins and co-workers²¹ reported that temporary improvement was produced by aureomycin in a patient with persistent *Escherichia coli* bacteremia and possible abdominal malignancy and infection, but the patient died of intestinal hemorrhage Spink and Yow³¹ obtained cure in a case of post-partum *E. coli* bacteremia responsive to no other therapy Dowling and colleagues³⁴ could not demonstrate any response to aureomycin therapy in 1 case with bacteremia

LUNG ABSCESS—Harvey, Mirick and Schaub⁴¹ gave aureomycin, 4 Gm daily for 20 days, to a patient with chronic *Escherichia coli* lung abscess, secondary to pulmonary adenocarcinoma Sulfadiazine and penicillin had proved ineffective Definite clinical improvement and disappearance of fever resulted, but surgical drainage later became necessary. At that time, the pus was found to be negative for coliform organisms, but proteus had appeared as a secondary invader

PERITONITIS—Several workers^{56 73 74} have reported on the value of aureomycin in peritonitis produced by *Escherichia coli* Yeager, Byerly and Holbrook⁵⁷ have treated 9 patients with *Escherichia coli* peritonitis, secondary to perforation of the appendix With appendectomy, drainage and aureomycin, all recovered Fine, Seligman, and Frank⁷⁵ state that it is the most effective drug available for the treatment of *Escherichia coli* peritonitis

SKIN AND SOFT TISSUE INFECTIONS—Two cases of *Escherichia coli* wound infection made a rapid clinical and bacteriologic recovery following the oral administration of aureomycin ³⁴

SINUSITIS—In 18 cases of sinusitis responding to aureomycin therapy, *Escherichia coli* was found to be one of the invading organisms, the others being staphylococci and streptococci (pp 15, 19) ⁴²

OTITIS MEDIA—Otitis media, in which *Escherichia coli* was cultured from 1 ear and staphylococcus from the other, which proved resistant to penicillin, cleared rapidly in 1 case treated by Whitlock ⁴⁴ This case has been discussed previously in connection with staphylococcal infections

OCULAR INFECTIONS—Clinical cure followed the local use of aureomycin borate in 1 case of *E coli* conjunctivitis ²⁵

Aerobacter Aerogenes—The successful treatment by Logan and co-workers of a case of *Aerobacter aerogenes* septicemia and meningitis has been mentioned by Wright and Schreiber ⁵¹ Prompt recovery under aureomycin therapy was observed by Dowling and his fellow-workers³⁴ in a tubo-ovarian abscess produced by *Aerobacter aerogenes* They reported rapid recovery in another patient with *Aerobacter aerogenes* urinary tract infection and septicemia Neter⁷⁶ has reported the cure of one case of meningitis A number of infections, particularly those of the urinary tract, in which this organism was one of several invaders, will be discussed under "Mixed Infections "

Pseudomonas Aeruginosa (*Bacillus pyocyaneus*) — Aureomycin has been thought to be ineffective against *Pseudomonas aeruginosa* and various members of the proteus group of organisms However, it has recently been shown to act on certain strains, and Neter, discussing a paper by Strax

and Wright⁷⁷ described a case of severe chronic pyelonephritis caused by this organism, which became sterile after treatment with aureomycin although sulfonamides, penicillin, streptomycin and mandelic acid had all failed. The use of a combination of streptomycin and aureomycin has been suggested by Alexander and co-workers.⁷⁸ Neter⁷⁶ has also described the cure of one case of pyocyanus meningitis in a child.

Salmonella Bacteremia—The evaluation of specific therapy in cases of salmonella bacteremia or enteritis is difficult. There seems to be a tendency for these organisms to entrench themselves as localized infectious foci in the bowel wall, thus becoming to a large extent immune to attack. Brainerd and associates⁴⁵ have reported excellent results from the use of aureomycin in *Salmonella schottmuelleri* septicemia in a fifteen-month-old boy, with negative blood cultures and normal temperature 48 hours after beginning treatment. In one fatal case of *Salmonella suispestifer* bacteremia,²¹ a large vertebrospinal abscess was found at autopsy.

ENTERITIS—Collins, Paine and Finland¹² obtained equivocal results with aureomycin in 5 cases of *Salmonella typhi* infection, only 1 showing unmistakable response to therapy, and also in 2 acutely ill patients with *Salmonella newport* enteritis, being effective in only 1 of the latter. All of the 5 typhoid cases were bacteremic, and in every case blood cultures became sterile and urine and stool cultures negative for *Eberthella typhi*, after 1 or 2 days of aureomycin administration. Clinical improvement was not cor-

respondingly rapid in 4 of these patients. In 9 cases of acute typhoid fever Brainerd and associates⁴⁵ obtained negative blood and stool cultures in 3 but without marked clinical benefit, but in 2 small children there was rapid response, with the attainment of normal temperature within 48 hours in 1 case and within 4 days in the other.

Dowling and co-workers⁸⁴ have reported similar doubtful effects in 8 cases of typhoid fever and 2 of salmonella enteritis. Alvarez⁷⁹ has seen good results with aureomycin in 3 cases of typhoid (doubtful in 2 others) and in 2 cases of paratyphoid A. Woodward⁸⁰ obtained no apparent benefit from its use in 4 cases of typhoid fever. Scarzella and associates⁸¹ found that *Eberthella typhi* disappeared from the stools in patients treated with aureomycin but that the clinical results seemed inconclusive. Knight and co-workers⁸² observed slight but definite benefit in some cases. Further work is in progress on the use of aureomycin in typhoid, since it is believed that certain strains are highly sensitive to this drug.

Shigella—Sulfadiazine has long been considered the drug of choice in shigella infections, although streptomycin has also been successfully used.

In 4 aureomycin-treated adult patients with *Shigella sonnei* dysentery, the temperature became normal, diarrhea ceased, and the stools became negative for *Shigellae* within 24 hours.³⁴ Although these results are evidently excellent, none of the patients was severely ill and the course of the disease may normally terminate by spontaneous recovery. Brainerd and co-workers⁴⁵ have treated

2 children with shigella dysentery, with prompt response to aureomycin

Pasteurella tularensis—Aureomycin is at least as effective in tularemia as is streptomycin, which has been considered specific for it since 1944.⁸³ The experience of Carroll and Gorman⁸⁴ with 1 patient would suggest that it is more effective. During a period of 10 days of streptomycin therapy, only slight subjective improvement had occurred, without fall in temperature. The day following the institution of aureomycin therapy, the patient felt decidedly better, and the temperature declined to normal within 36 hours.

Woodward^{80, 83} noted in 3 cases marked reduction in toxemia and cough within 24 hours, with simultaneous increase in strength and appetite. Prompt recovery also took place in these 3 seriously ill patients. One was of the ulceroglandular and 2 were of the typhoidal variety. The results obtained by Ransmeier, Price and Barnes⁸⁵ were similar, in 1 case of severe tularemic pneumonia and 1 case acutely ill with the ulceroglandular form of the disease and marked sepsis. Both exhibited rapid response to aureomycin within 24 hours. A third case also responded well, but suppuration occurred in an axillary node.

The rare oculoglandular form of tularemia responds to aureomycin with the same promptness as do the commoner varieties. Lindeke and Maiden⁸⁶ have reported what is apparently the first case treated with this antibiotic. The ocular, glandular and systemic manifestations showed improvement within 24 hours and the tempera-

ture dropped to normal in 12 hours and remained so. One week later, there were only very slight residual manifestations which disappeared within the next month.

Hemophilus—In a case of *Hemophilus ducreyi* infection of 2 months' duration, complete relief from pain, soreness, and consequent difficulty in walking was experienced on the day after aureomycin treatment was begun.⁸⁷ Cure was apparently complete by the seventh day. With sulfonamides, 2 or 3 weeks' treatment is often necessary. Brainerd and associates⁴⁵ also observed rapid healing of chancroidal ulcers and reduction of inguinal adenitis in a case of chancroid. Zheutlin and Robinson⁸⁸ obtained cure in 3 proven cases of chancroid. They recommend that the use of aureomycin for this infection be followed by repeated examinations for several months to exclude the possibility of "masked" syphilis.

MENINGITIS—Until recently the therapy of *Hemophilus influenzae* meningitis included the combined use of streptomycin and sulfadiazine and, in severely ill patients, of antiserum as well. Yampolsky and Jones⁸⁹ believe that antiserum is not needed in the majority of cases.

Chandler and Hodes⁹⁰ have reported 6 cases in children of *H. influenzae* meningitis, treated with aureomycin, of whom 5 recovered and 1 died. Of the 5 cases that recovered, 2 were treated with aureomycin and sulfadiazine, 3 were treated with aureomycin alone. The patient who died was admitted to the hospital in a moribund condition, after an illness of only 13 hours' duration. He was given both aureomycin and sulfadiazine, but death

occurred within 36 hours of admission. All cases received aureomycin intravenously and orally except the last, who received it per rectum in place of orally.

Bean and Ross⁹¹ have reported the successful use of aureomycin in conjunction with sulfadiazine in a severe case of *Hemophilus influenzae* meningitis in a two-year-old child. The patient was unable to retain oral doses, and continuous intravenous drip was therefore used, delivering about 1 Gm daily for 8 days, and sulfadiazine was given parenterally. The spinal fluid culture became and remained negative after 24 hours of treatment. Progressive clinical improvement began on the fifth hospital day, and on the thirteenth day he was able to sit up in a chair. Residual disturbance of gait was present 3 months later.

It is not possible to give a definite opinion as to the value of aureomycin in such cases, but it can probably be used with advantage for patients showing toxic reactions to streptomycin or for cases in which the organism has become streptomycin-resistant. Except in very mild cases in older children, sulfadiazine should be given as well.

OCULAR INFECTIONS—Clinical cure followed the local use of aureomycin by Braley and Sanders²⁵ in 4 cases of *Hemophilus influenzae* conjunctivitis.

PERTUSSIS—Experimentally, Bradford and Day⁹² found that aureomycin has a bacteriostatic effect on *Hemophilus pertussis*, and that daily doses of 10 and 100 mg per kilo per day protected mice given intranasal instillations of 250 MLD of the organism.

The course of human pertussis is favorably modified by aureomycin, with reduction in the frequency and

intensity of paroxysms Bell, Pittman and Olson,⁹³ reporting 20 cases, found that if aureomycin was started early in the disease, prompt recovery followed a few days of treatment, which could be given at home, and that in others aureomycin shortened the course of the disease

Knight⁹⁴ reported on 6 cases of pertussis in infants treated by Drs Miller and Ross, who noted improvement, with disappearance of cyanosis and vomiting, in all the children within 3 or 4 days after starting aureomycin, and cessation of whooping within a week or 10 days.

Brucella—The treatment of brucellosis has, until recent years, been very unsatisfactory Heat-killed vaccines and bacteria-free filtrates and the sulfonamides have been tried, with little success The high incidence of chronic illness arising from this disease makes its cure a problem of great importance The introduction of combined sulfadiazine and streptomycin (or dihydrostreptomycin) therapy was hailed as a great forward step, and now aureomycin bids fair to supplant this

An increasing number of favorable reports^{83,84 41 67,79,80 95-101} on the aureomycin treatment of brucellosis indicates that the antibiotic is of great value in brucella infections, even in chronic cases Knight and co-workers¹⁰² obtained prompt response and complete remission in 4 acute cases treated by them, including 1 with meningo-encephalitis, but found no apparent effect in 1 chronic case, which was afebrile at the time. Complete recovery was observed by Harris¹⁰¹ in 89 per cent of 110 cases of chronic brucellosis. Side reactions in this group of patients were more marked

than in other reported series

Spink and his colleagues¹⁰³ treated 24 cases, acute and chronic, with aureomycin and observed prompt response in all. The addition of sulfadiazine did not improve the results, which were superior to those following combined therapy with streptomycin and sulfadiazine. This agrees with the findings of other workers.^{20 104} Herrell and Barber¹⁰⁵ have found both *Brucella suis* and *Brucella abortus* to be susceptible to aureomycin and believe a combination of aureomycin and dihydrostreptomycin to be the optimal form of therapy. Debono¹⁰⁶ has successfully treated 24 cases, 20 of which had positive blood cultures for *Brucella melitensis*. Machado and Saraiva¹⁰⁷ have reported excellent results in 2 additional cases of Malta fever. Boyd and Prignano¹⁰⁸ have reported the case of a nine-year-old girl with *Brucella abortus* bacteremia, who had been given a combination of penicillin and streptomycin without benefit, and whose symptoms completely disappeared without recurrence, after 4 days of aureomycin therapy.

There is some tendency toward relapse after treatment has been stopped, and Knight and his fellow-workers¹⁰⁹ consider further evaluation of dosage schedules in relation to final results to be indicated.

Debono¹⁰⁶ has drawn attention to a phenomenon frequently occurring at the beginning of aureomycin treatment, at least in cases of *Brucella melitensis* infection. An initial rise in temperature on the first day, persisting for 1 or 2 days, is followed by a precipitous fall. The decrease in fever is usually preceded by marked clinical improvement and sterilization of the blood stream. It is possible

that small initial dosage will obviate this. The rheumatic involvement so frequently associated with brucellosis did not develop in any of his 24 patients during convalescence. One patient with coxitis and 1 with sacroiliac arthritis had almost immediate relief of pain and very rapid recovery. He considers that reported treatment failures can be attributed to inadequate dosage, and recommends 250 mg. every 3 hours for 12 to 14 days.

Rosenbaum and Reveno¹¹⁰ agree that aureomycin is specific for brucella infections, but believe that a combination of aureomycin with dihydrostreptomycin will give even better results, by permitting smaller doses of aureomycin and thus reducing the tendency to gastrointestinal disturbances. They have reported 2 cases thus treated, one of whom would otherwise have been a failure, and both of whom recovered promptly with no relapse during observation periods of 5 and 8 months respectively. Eisele and McCullough¹¹¹ used a combination of aureomycin, dihydrostreptomycin and sulfadiazine in the successful treatment of 1 case.

Harris¹¹² has made a study of the side effects of both aureomycin and chloramphenicol in brucellosis. He has noticed a definite sex influence, about 3 women showing untoward reactions to every 1 man, and suggests that estrogen deficiency may develop during treatment. This idea receives support from the cases of 2 women undergoing aureomycin therapy, who developed a vaginitis relieved by a single parenteral dose of estrogens. Both aureomycin and chloramphenicol have been shown to have a profound effect on the bacterial flora of the intes-

tine, the normal odor of the stool disappearing in 50 per cent of cases, within 1 to 3 days after beginning treatment with 2 to 4 Gm of either daily Mucous membrane and dermal lesions resembling those of vitamin B complex deficiency, particularly that of riboflavin, developed in some of the women patients and in a few of the men. In 7 females, there were some indications of vitamin K deficiency. Urinary frequency was noted in 7 per cent or 8 per cent (all females) of the patients receiving either drug. Brief Herxheimer reactions were observed in 2 of the 135 patients treated with aureomycin.

Harris¹¹² recommends that vitamin B complex be given even when aureomycin is being administered intravenously, since this antibiotic is probably excreted into the bowel after intravenous injection.

Bacteroides—SEPTICEMIA—Cases of septicemia produced by *Bacteroides funduliformis* have been successfully treated with aureomycin by McVay, Guthrie and Sprunt.¹¹³ It is probable that a number of cases of this type of infection go undiagnosed when routine blood cultures are made, since these organisms are anaerobes, and anaerobic techniques must be used in their study.

Pleuropneumoniae Group — ARTHRITIS — Experimentally, aureomycin has been found to prevent the development of arthritis in rats and mice infected with “pleuropneumonia-like” organisms.^{114,115} It has been found¹¹⁶ to cause the disappearance of such organisms from the genitourinary tract of patients with various, perhaps related diseases,

with or without joint involvement, i e , rheumatoid arthritis, erythema nodosum, rheumatic fever, nonspecific urethritis, Marie-Strumpell spondylitis Results were good in 17 out of 25 cases of rheumatoid disease, and compare favorably with those following gold therapy Kuzell, Gardner and Fairley¹¹⁷ found it of doubtful value in 4 advanced cases of rheumatoid arthritis refractory to other treatment, but obtained dramatic relief in 1 patient with Reiter's disease as did also Carroll and co-workers ¹¹⁸

URETHRITIS—Willcox and Findlay⁶⁹ obtained cure with aureomycin in 3 cases of nonspecific urethritis in which organisms of the pleuropneumonia group were present Finland, Collins and Paine¹¹⁹ also noted good results in 1 case in which these organisms were cultured from the urethra and which had not responded to repeated courses of penicillin, streptomycin and sulfonamides Aureomycin produced symptomatic relief and negative cultures in 3 days

Donovania Lymphogranulomatis (GRANULOMA INGUINALE)

—Aureomycin exhibits therapeutic activity in all of the 5 venereal diseases, of which granuloma inguinale is one Advanced cases of this infection have often resisted all forms of therapy before the introduction of streptomycin, which produced an over-all cure rate of about 75 per cent in ambulatory, and 90 per cent in hospitalized, cases. Disadvantages in the use of streptomycin are its toxic effects, the necessity for intramuscular injections and the development of drug resistance or drug dependence Greenblatt and associates¹²⁰ have obtained cures with oral

aureomycin in 16 cases of granuloma inguinale, 5 of whom were streptomycin-resistant. Four patients given parenteral aureomycin failed to improve. They consider that 20 Gm, given over a period of 10 days, is the minimum effective dose, but that severe cases should be treated longer and more intensively.

Wright and co-workers^{121, 122} successfully treated 13 cases, with rapid healing of all lesions and with no recurrence 6 months after treatment. Greenblatt and associates¹²³⁻¹²⁵ have reported 47 cases, and Robinson and co-workers¹²⁶ have reported 42 cases. In this latter group, streptomycin and antimonials had proved ineffective in several cases, but all responded in a spectacular manner to aureomycin.

An additional 9 cases of 10 to 16 years' duration, reported by Hill, Wright and co-workers²³ uniformly showed complete healing of the lesions and cessation of discharge. The length of treatment varied from 15 to 62 days. Administration was by various routes, oral, intramuscular and intravenous dosage was used, singly or in combination. Intravenous aureomycin seemed to produce more rapid healing of the ulcers. Greenblatt and co-workers¹²⁰ experienced their only failures, in 4 out of 16 cases, when intramuscular dosage was used, but these patients readily responded to oral therapy. If surgery is indicated, it should be combined with aureomycin therapy. Treatment should be continued until beginning healing is definite. The healing process is complete within about 11 days after the end of therapy, the Donovan bodies disappearing in 3 to 9 days.

Rickettsial Infections

The record of aureomycin to date in the treatment of rickettsial infections is uniquely excellent. The successful treatment of these diseases for which no completely satisfactory therapy has hitherto been available, has been reported from all parts of the world. Cutileiro and co-workers¹²⁷ in Portugal have reported the efficacy of aureomycin in European rickettsioses, and Benhamou and his associates¹²⁸ have found it effective in typhus and boutonneuse fever, which occur both in France and in North Africa and their electrophoretic studies of the blood globulins indicate that aureomycin has a specific effect on rickettsial disease. Dole and co-workers¹²⁹ had previously found by electrophoresis a marked reduction in albumin and in A/G ratio with increase of globulin, from the fourth day of typhus through convalescence.

Rickettsia rickettsii

ROCKY MOUNTAIN SPOTTED FEVER—Rocky Mountain spotted fever is a very severe acute infection. In those regions where it is prevalent the mortality rate at present is higher than that of any other common infectious disease. Sulfonamides only intensify the severity of the infection, penicillin and streptomycin are of no value. Aureomycin which attacks the rickettsiae within the cells is superior to any treatment previously tried, including that with para-aminobenzoic acid. The prognosis is improved in even the most severe cases and becomes very good for the average attack if treatment is begun within a week of onset.

Harrell¹³⁰ remarks that we have now entered upon a new era in the treatment of this disease, and a large number of cases have already been successfully treated with aureomycin ^{6 16 20 32 41.131-133}

In a series of 8 cases treated by Dowling and co-workers³⁴ there was only 1 failure, in a comatose patient with congenital ichthyosis, treated on the ninth day of his illness. The average duration of fever after the first dose was 3.6 days. The incidence of complications has been very low in aureomycin-treated cases, and satisfactory results have been obtained even when treatment has been started late in the course of the disease, when the patient appears to be dying.^{134 135} Ross and associates,¹³² who published a report on 13 treated cases, found only 2 in which supportive therapy was needed. Aureomycin was not begun until the eighth day of the disease in both patients. Definite response to treatment was noticed, as a rule, within 24 hours, followed by disappearance of the rash within the next few days. In patients treated before the fifth day of illness, the eruption did not become petechial.

Rickettsia Tsutsugamushi

According to unpublished Army reports referred to by Woodward,⁸⁰ aureomycin is effective in scrub typhus.

Rickettsia Mooseri

The results of aureomycin treatment in murine typhus are similar to those obtained in Rocky Mountain spotted fever.

Woodward⁸⁰ has reported good response in murine

typhus to aureomycin in 1 case and Hill¹³⁵ in 8 cases of this infection Knight, Ruiz-Sánchez, Ruiz-Sánchez and McDermott¹⁰² gave aureomycin to 19 patients, with prompt reduction of temperature and complete recovery in all cases. Dramatic improvement and prompt clinical remission was noted by them in a further series of cases¹⁰⁹ and they conclude that aureomycin is highly effective in typhus Sánchez and Sánchez¹³⁶ have remarked that the clinical picture returns almost to normal in the first 36 hours of aureomycin treatment and that the shortening of the course of the disease is proportional to the promptness with which therapy is begun. Benhamou¹²⁸ notes that in murine typhus in North Africa, which is usually a mild disease, even when untreated, the temperature is normal in less than 48 hours following administration of aureomycin.

Epidemic typhus fever (including the recrudescent form, Brill's disease) has been successfully treated with aureomycin^{80,137-139} with rapid and complete clinical response Benhamou and his group¹²⁸ reporting similar results, state that the response is rather slower than in murine typhus It is probable that this antibiotic may be considered a specific for epidemic typhus

Rickettsia rickettsii var. *pijperi*

Three cases of tick-bite fever which recovered rapidly on aureomycin therapy have been reported in South Africa.^{140 141} Disappearance of fever within 14 hours, and of all symptoms within 24 hours, following administration of aureomycin has been recorded¹⁴¹ in 1 of these cases The

patient had been ill for a week previously, but was well enough to attend to his business 72 hours after beginning treatment.

Coxiella burnetii

Aureomycin is considered to be specific for Q fever ¹⁴³ It is particularly valuable when employed early in the disease, before there has been time for definite serologic diagnosis, so that it must often be given on mere suspicion of Q fever. However, since it produces no interference with antibody formation, a positive diagnosis can be made serologically, even after recovery ¹⁴³ Lennette, Meiklejohn and Thelen¹⁴⁴ obtained good results in 14 acute cases given aureomycin orally, but less satisfactory response in chronic cases.

An additional 15 cases were treated by this group⁴⁵ with satisfactory response. The general consensus is that aureomycin is a highly satisfactory remedy for infection by this organism ^{34,40,145}

Rickettsia akari

Although rickettsialpox is a nonfatal disease, and the need for a specific therapeutic agent is less urgent than in other rickettsial infections, there may be acute illness with severe constitutional symptoms for a week or more.

In 2 cases of rickettsialpox treated with aureomycin,¹⁴⁶ there was a precipitous fall of temperature to normal levels within 24 hours of receiving the first dose. Disappearance of fever coincided with disappearance of symptoms and signs of disease.

Infections Caused by Viruses and Virus-like Organisms

Generalized Infections

PRIMARY ATYPICAL PNEUMONIA—Aureomycin is now being widely used for the treatment of the nonbacterial pneumonias ¹⁴⁷ Good to excellent results have been reported by a large number of observers ^{20,34 80 148-156}

Before the introduction of aureomycin, no known therapeutic agent was capable of altering the course of the disease. Fortunately, in most cases, the infection is of only mild or moderate severity and tends to recovery. Aureomycin appears to be the only drug that will exert a favorable influence in all cases. Herrell¹⁴ has described impressive response to aureomycin therapy in a group of 14 patients. Frohman and Elkins¹⁵⁶ gave aureomycin to a critically ill nineteen-year-old girl with remarkable effect. She was going rapidly downhill, in spite of treatment with penicillin and sulfadiazine, and was cyanotic, dyspneic and delirious, with internal strabismus. At the time of starting aureomycin, the patient appeared to be dying. Two hundred fifty mg every 4 hours was begun at 2 P M., and at 11 P M she was rational and breathing more easily. Within 48 hours, the temperature was normal and the chest nearly clear. Daily blood transfusions of 200 cc. each were also given for the first 3 days.

Prompt initial symptomatic improvement and disappearance of fever resulted from aureomycin administration in 14 of 16 patients reported by Brainerd and co-workers,⁴⁵ with roentgenologic evidence of pulmonary involvement.

Several of them had been extremely ill, and penicillin had been without effect on their condition. These authors look on aureomycin as the preferred drug in nonbacterial pneumonia.

In a controlled series of cases of primary atypical pneumonia, Meiklejohn and Shragg¹⁵⁷ obtained evidence that aureomycin has a definitely beneficial action in this condition. Dingle and co-workers¹⁵⁸ recommend that further controlled study be carried out on its therapeutic effects.

Collins and co-workers¹⁵⁹ have endeavored to make an accurate assessment of the value of aureomycin in 40 cases of primary atypical pneumonia. Previous work had shown that the variable course of the illness when treated with penicillin, as contrasted with the quite prompt and regular improvement when aureomycin was given, indicated that the latter had a specific influence on this infection.

In every one of their patients, definite improvement occurred during the first day or two of aureomycin therapy, but in one-third of these, the improvement may have been coincidental. The response of the remaining two-thirds, however, could with confidence be ascribed to aureomycin, and in many cases its rapidity and extent were very striking. The authors believe that the beneficial effect of aureomycin on patients with primary atypical pneumonia has been convincingly, if not absolutely conclusively, demonstrated.

INFLUENZA—Finland and co-workers⁵⁸ treated 18 acutely ill cases of influenza A, with varying degrees of pulmonary

involvement, by means of aureomycin. All had the clinical and laboratory findings typical of influenza, in only 2 was the attack a mild one.

An impressive degree of improvement was produced by administration of the antibiotic and it was, if anything, even more striking than that seen in pneumococcal or primary atypical pneumonia. In every case, the first 36 hours witnessed a marked and sustained drop in temperature, which occurred within 24 hours in 16 of the cases. All but 3 were permanently afebrile within 48 hours. Symptomatic improvement kept pace with the drop in temperature, even in one case complicated by a benign lymphocytic meningitis. In most of the cases, the lungs were clear to X-rays before the fifth day of treatment.

A group of 10 patients clinically resembling the previous group, but without pulmonary lesions, and without serological or cultural evidence of the influenza virus, was also given aureomycin. All were seriously ill, with temperatures between 102° and 104° F. In all but 2 the fever disappeared permanently, with concurrent symptomatic relief, within 12 to 24 hours. The 2 exceptions had a slight return of fever (99.4° F) during the second day. In 1 of the cases, an *Escherichia coli* urinary infection cleared up within 2 days.

In a heterogeneous group of 13 patients⁵³ with pneumonia of undetermined etiology, aureomycin produced very definite beneficial results. Five cases of pneumonia secondary to other serious conditions failed to respond significantly, although 4 of them were later given massive dosage of penicillin in addition to aureomycin.

For the acute bronchiolitis, or "viral" pneumonitis, of infants, aureomycin appears to be somewhat more effective than other forms of treatment currently being used. Thompson and Spector¹⁶⁰ compared the course of 32 patients receiving aureomycin with that of an equal control group receiving penicillin, sulfadiazine, streptomycin, or some combination of these. Of the aureomycin group 49 per cent were afebrile in 24 hours, as against 43.7 per cent of the control group.

LYMPHOCYTIC CHORIOMENINGITIS—This acute virus disease usually tends to recovery, with few complications—a fortunate circumstance—since hitherto treatment has been purely symptomatic. Aureomycin caused striking relief of symptoms in 2 cases of lymphocytic choriomeningitis treated by Grater and Rider.¹⁶¹ Meningeal signs and symptoms showed a definite decrease within 24 hours and had disappeared, with reduction of the temperature to normal, in 96 hours.

PSITTACOSIS (*Ornithosis*)—A case of psittacosis reported from Alabama,¹⁶² which had failed to respond to penicillin, improved rapidly when the dosage of penicillin was increased and aureomycin given simultaneously. Dramatic results from the use of aureomycin have been reported by Woodward⁸⁰ in a case of ornithosis contracted from pigeons and characterized by bilateral pneumonitis, severe headache, and toxemia. Brainerd and co-workers⁴⁵ have treated 3 cases of psittacosis which responded poorly to penicillin but well to aureomycin and believe the latter to be the indicated remedy in this infection.

INFECTIOUS MONONUCLEOSIS—Three cases of infectious

mononucleosis treated with aureomycin have been observed by Dowling and co-workers³⁴ In 2 cases, there was marked symptomatic and objective improvement, with normal temperatures, within 48 hours The third case was apparently a mild infection and the effect of aureomycin could not be assessed Lyons¹⁶³ has also reported 3 cases, with normal temperatures and symptomatic cure within 24 hours after starting treatment He stresses the probable value of such therapy in the prevention of severe visceral and nervous system complications In a case with hepatic involvement treated with aureomycin, all abnormal functional tests became normal, with disappearance of hepatomegaly and splenomegaly, within 10 days Spink and Yow³¹ have reported favorable results in 7 cases Favorable response in an additional case with cough, splenomegaly and toxicity has been observed by Gruskin¹⁶⁴ Wright and Schreiber⁵¹ observed early improvement in 1 case, but the course of the disease was not shortened Several other workers^{45,165-167} have reported inconclusive results in this infection In general, we may say that apparently aureomycin is useful in some cases of this infection

LYMPHOGRANULOMA VENEREUM—Good results have been obtained in a number of cases of lymphogranuloma venereum treated with aureomycin^{34,41,168} It has an excellent effect both on the primary infection and on secondary invaders The results reported by Wright and co-workers^{22,121,122} appear to be representative of those noted by other observers They found decided regression of buboes and marked clinical improvement after 4 days of therapy Patients with proctitis evidenced healing of mu-

cosal lesions, and those with benign rectal stricture experienced decided relief from pain and bleeding, with increase in the diameter of the stools. One patient with a rectovaginal fistula became asymptomatic after 14 days of treatment. Aureomycin will not, of course, do away with the need for surgery in severe anatomic abnormalities produced by this infectious agent, but is considered the treatment of choice insofar as medical management is concerned.

In order to ascertain whether a "carrier" state was likely to exist after treatment, Runyan, Kraft and Gordon¹⁶⁹ attempted to demonstrate the persistence of virus in healing buboes. After the first 3 days of aureomycin administration, they were unable to detect the presence of an infecting agent.

MEASLES—The response of 9 cases of measles to aureomycin therapy, as reported by Dowling and his fellow-workers³⁴ and the report of 12 cases by Drake and co-workers,¹⁷⁰ are encouraging, but the series are too small to permit the drawing of definite conclusions.

Ocular Infections

Excellent response to local aureomycin has been noted²⁶ in eye infections, such as follicular, inclusion and vernal conjunctivitis, epidemic keratoconjunctivitis, uveitis, dendritic keratitis, and trachoma. deRoethth¹⁷¹ has shown that aureomycin penetrates into the eye less readily than other antibiotics, but that once it has crossed the blood-aqueous humor barrier, it remains longer in the ocular fluids and tissues.

EPIDEMIC KERATOCONJUNCTIVITIS—Holmes¹⁷² has found a combination of aureomycin ophthalmic and fifteen per cent sulfacetamide, with 1 3000 mercury bichloride ophthalmic ointment to be of most value in epidemic keratoconjunctivitis, but notes that this treatment has not prevented the formation of corneal infiltrates

DENDRITIC KERATITIS—Appelman and Hale¹⁷³ have reported speedy control by aureomycin of symptoms and of ulceration in an extremely obstinate case of dendritic keratitis of 4 year's duration, which was undergoing an acute flare-up at the time of beginning treatment with aureomycin.

Skin Infections

HERPES SIMPLEX—Kalz and co-workers¹⁷⁴ have used aureomycin in a water-soluble methyl cellulose base, as a local "film" dressing, in 6 cases of herpes simplex and in 1 with cutaneous and oral herpes. Good results were obtained in all cases after 1 application to the skin, and, in the stomatitis case, after several to the tongue. All symptoms disappeared within 24 hours and the vesicles healed completely within 48 to 72 hours. The film is painted on in several layers and is easily removable with water.

Hollander and Hardy⁴⁷ have reported a case of herpes simplex of the neck. Pain ceased almost at once after the application of an ointment containing 3 per cent of aureomycin hydrochloride and recovery was complete in 5 days. The same authors¹⁷⁵ have used 3 per cent aureomycin ointment locally in 11 consecutive cases of "cold sore" on the lips. Applications were made frequently, so as

to keep the involved area covered at all times. Very marked relief of pain and tenderness resulted in all patients, with definite shortening of the duration of the attack.

KAPOSI'S VARICELLIFORM ERUPTION (*Disseminated cutaneous herpes simplex*)—In a febrile toxic case of this infection, aureomycin produced rapid disappearance of fever and of cutaneous lesions and appeared to shorten the period of illness. Bereston and Carliner,¹⁷⁶ who reported this case, brought forward evidence in support of the view that this condition is caused by the virus of herpes simplex. A patient treated by Bockman¹⁷⁷ was almost completely cured within 48 hours. Baer and Miller¹⁷⁸ have observed rapid healing in 2 additional cases, 1 with mucosal lesions as well. Penicillin and bacitracin ointment had not been able to check the spread of the eruption.

ECZEMA VACCINATUM—A severe case of eczema vaccinatum, in a two-year-old child, developing 4 days after exposure to a healing vaccination scar, responded promptly to aureomycin according to Perry and Martineau.¹⁷⁹ Penicillin and boric acid compresses for 2 days had produced no apparent improvement. Within 24 hours after beginning aureomycin, recession and drying of the vesicles was obvious and 48 hours later the temperature, which had been as high as 104.8° F, became normal. There was scarcely any residual scarring when the child was discharged on the eleventh hospital day. The vesicles were typical of a vaccinia lesion, with little secondary infection. It is possible that a similar therapeutic effect might be obtained in smallpox.

DERMATITIS HERPETIFORMIS—Quicker and more satis-

factory response was observed in 5 cases of dermatitis herpetiformis¹⁸⁰ to aureomycin than to any other type of treatment. Marked relief of itching and involution of the vesicles occurred within 1 or 2 weeks. There was a tendency to slight recurrences after treatment had been stopped. Saffron,¹⁸¹ reporting good results in 2 additional cases in children, agrees that aureomycin is superior to any other medication.

MOLLUSCUM CONTAGIOSUM—Dramatic response to aureomycin therapy has been reported by Guy, Jacob and Guy¹⁸² in a case of generalized molluscum contagiosum. The drug was given for 2 days, 250 mg twice daily. Two weeks after beginning treatment, only pigmented macules remained. The authors suggest the use of aureomycin in other warty conditions, but the experience of Beinhauer and Gibson¹⁸³ with 22 cases of verruca vulgaris has not been encouraging.

PEMPHIGUS—The etiology of pemphigus is unknown. Possible etiologic agents are streptococci and a filterable virus. Up to the present time, most cases of toxic pemphigus have died regardless of the type of therapy employed. In aureomycin, it would seem as if we had, for the first time, an effective remedy. Natenshon¹⁸⁴ has presented a typical case, with staphylococcus septicemia, which responded to prolonged therapy (5 months) with aureomycin. Bettley¹⁸⁵ has reported another case in which recovery was apparently the result of aureomycin administration. The prognosis was grave when treatment was begun, but within 24 hours, a striking improvement set in. The temperature remained normal after the third

day and no fresh blisters appeared after the first dose.

HERPES ZOSTER—The results of aureomycin therapy in 24 cases of herpes zoster treated by Finland and associates¹⁸⁶ suggest very strongly that aureomycin, 4 Gm daily, has a definitely beneficial effect in this condition, particularly when treatment is begun early. In most of the patients there was no evidence of secondary bacterial invasion and no new lesions developed after the first day or so of treatment. Pain was relieved after the first day. When the lesions had all dried, half the dose of aureomycin was given for another 3 to 5 days

The remark of a colleague to the effect that one of his patients, who had herpes zoster and who was given aureomycin for another condition, experienced dramatic relief of the herpes within 24 hours led Binder and Stubbs¹⁸⁷ to administer it to 4 patients with this disease. Striking results were obtained in 3 of them and good, although less rapid, response in the fourth. It is of interest that one of these cases, an eleven-year-old child, developed poliomyelitis 5 days after subsidence of the rash. The dosage scheme used was 500 mg (adults) or 250 mg (children) every 6 hours for 2 days. Good results were also noted in a patient reported by Case¹⁸⁸. Brainerd and his associates⁴⁵ noted dramatic improvement in 1 case of herpes zoster ophthalmicus. It is apparent that further work in this field is indicated.

Spirochetal Infections

Treponema Pallidum

Although *in vitro*, aureomycin has very much less immobilizing effect on *Treponema* than has penicillin, it has been effective in experimental syphilis, both in prophylaxis and in treatment of early infection. Wiggall, Zheutlin and associates,¹⁸⁹ in addition to this experimental work, have reported a case of secondary syphilis and granuloma inguinale, who was given aureomycin for the latter condition. Within 72 hours, the syphilitic condylomata lata had become dark-field negative and had begun to involute. They gave aureomycin to 15 additional patients, all with positive dark-field findings, 8 primary and 7 secondary with condylomata lata. Nine cases received 2 or 4 Gm daily for 2 days and 6 received 4 Gm daily for 6 days. At the end of the study period, all were given 4-8 million units of penicillin.

In the first group, 4 of the 9 patients had become dark-field negative within 48 hours, and the others had a reduced count of *Treponema pallidum*. All of the second group were dark-field negative at the end of 72 hours and remained negative for observation periods of 72 to 144 days.

In 2 cases of acute, dark-field positive syphilis treated with aureomycin by O'Leary and co-workers,¹⁹⁰ and in 2 cases of late nodulo-ulcerative syphilis,¹⁹¹ aureomycin produced definite improvement. The early cases became dark-field negative within 60 hours and primary lesions healed in about 16 days. Healing of nodular and ulcerative lesions took place in the chronic cases.

One of the patients with early syphilis developed signs of vitamin B deficiency, probably due to interference with bacterial synthesis. The authors routinely administer vitamin supplements to patients receiving aureomycin.

In a further report on the above patients,¹⁹² it is noted that the spinal fluid and the blood serology of the 2 early cases were completely negative 4 months after treatment, and that in the late cases there was some decrease in the serology but no significant reversal.

O'Leary¹⁹² has reported encouraging but inconclusive results in neurosyphilis. In active infection of the spinal fluid, aureomycin tends to return the cell count to normal about as rapidly as does penicillin. The clinical manifestations are less definitely affected.

Irgang and Alexander¹⁹³ have also observed favorable responses to aureomycin in 9 cases of early syphilis and believe that this drug may prove to be curative in fusospirillary diseases of the skin.

Clinical work on aureomycin in syphilis is still in the experimental stage. It seems to produce a satisfactory initial decline in serologic titer and sterilizes surface lesions in about 40 hours.¹⁹⁴ Willcox¹⁹⁵ has obtained gratifying clinical results and recommends further trial of aureomycin in syphilis. Aureomycin is not indicated for the treatment of syphilis at the present time. Additional work in progress may change this situation.

Borrelia

In a case of acute ulceromembranous stomatitis,¹⁹⁶ which developed following repeated attacks of acute herpetic

gingivostomatitis, and which failed to improve on penicillin, aureomycin brought about rapid recovery. It was given in doses of 0.5 Gm. every 6 hours for about 2 days, then every 12 hours, to a total of 9.0 Gm. The temperature was normal within 4 hours of the first dose and the patient felt better. By the next day, the lesions were involuting with disappearance of oral fetor.

Spirillum Minus

As reported by Wright and Schreiber,⁵¹ Logan and associates have successfully treated a case of rat-bite fever with aureomycin, after the failure of penicillin and streptomycin.

Leptospira Icterohemorrhagiae

Although leptospirae have been found experimentally to be inhibited by aureomycin, only 1 case⁴⁸ in man has so far been treated in this country with this antibiotic. The patient, a sewer worker, who was brought into the hospital unconscious on the fourth day of his illness, was treated with intravenous and oral aureomycin. Recovery was satisfactory and prompt. Lurie¹⁹⁷ has reported cure of 1 case in the Orient.

Fusospirochetosis

Greenblatt and associates¹²⁵ find that fusospirochetosis (Vincent's infection), which is found in association with granuloma inguinale in about 21 per cent of patients, responds well to penicillin and more slowly to streptomycin, aureomycin or chloramphenicol.

Protozoal Infestations

Recently there have been indications that aureomycin may have definite curative value in protozoal invasion and perhaps also in helminthic infestations.¹⁹⁸

Endameba Histolytica

McVay, Laird and Sprunt¹⁹⁹ were led by the observed effects of oral aureomycin on intestinal lesions and on the bacterial flora of the intestine to try it in the treatment of 14 cases of amebiasis. The preliminary results were encouraging and negative stools were obtained in the 3 cases which were reported in detail. Aureomycin is believed to be effective in intestinal amebiasis, but should not be used alone for the systemic form of the disease. MacDonald²⁰⁰ has reported cure in another case.

Trichomonas Vaginalis

Suppositories of aureomycin have been used in cases of trichomal vaginitis by Greenblatt and West²⁰¹ with good results. *In vitro*, aureomycin and tyrothricin have far greater trichomonicidal potency than have chloramphenicol, penicillin and streptomycin, although the last named has been found to give better clinical results than any previously used remedy.

Infections of Undetermined Etiology

Aureomycin has been found effective in a variety of infections whose origin was undetermined bacteriologically, or not stated. These include mastitis,³⁴ sinusitis,⁴¹ rodent ulcer,⁴¹ chronic ulcerative colitis,^{34, 41} rat-bite fever,⁴¹ bron-

chiectasis,³⁴ regional ileitis,⁵¹ post-cholecystectomy syndrome,^{57,77} compound fractures,³⁴ oral sepsis²⁰² and appendiceal abscess.⁵⁷

Mixed Infections

Certain types of infections have a marked tendency to a mixed etiology. This is particularly true of those affecting regions of the body in close proximity to the alimentary canal, e g , the mouth, the peritoneum, the genitourinary system. Before the advent of aureomycin, a multiple form of therapy was generally employed, using the drugs best suited to each of the organisms present. Since aureomycin appears to be highly effective against most of the commonly found bacteria and since there is little tendency toward the development of resistant strains, it would seem to be the most valuable remedy available for such mixed infections.

PERITONITIS AND INFECTIONS OF THE ABDOMINAL WALL—Herrell¹⁴ has pointed out that the wide therapeutic range of aureomycin and its freedom from harmful effects render its use suitable for the prophylaxis of peritonitis, as well as for its cure. Wright and co-workers⁵⁶ have found that, in the therapy of acute peritonitis, optimum results were obtained by a combination of oral and intravenous aureomycin administration. The only deaths⁴ in their series of 52 cases occurred in patients given aureomycin by mouth alone. One of these deaths was from pulmonary embolism.

The peritonitis was the sequel to appendicitis (generally with perforation), perforated gastroduodenal ulcer, or perforated diverticulum, and *Escherichia coli* was the

predominant organism, with other bacteria present in all but 1 case. The other invaders included various strains of streptococcus, paracolon bacilli, *Bacteroides funduliformis* and *melaninogenicus*, *Micrococcus pyogenes*, hemolytic and nonhemolytic *Staphylococcus albus*, *Clostridium perfringens* and *tetanosporum*, *Aerobacter aerogenes*, *Corynebacterium pseudodiphthericum*, and *Klebsiella pneumoniae*.

All but 1 of the patients were operated on, with drainage in 95 per cent of the cases. Only minimal toxic reactions were observed. Mild to moderate phlebitis developed after intravenous injection, in 10 cases, but did not interfere with recovery. The mortality was very definitely reduced (50 per cent) from that in previous series in the same hospital and the authors believe aureomycin to be of significant value. Since then they⁷⁷ have treated 7 more patients with no deaths

Yeager and co-workers⁷⁸ reported similarly good results with aureomycin in 1 case of peritonitis (*Escherichia coli* and *Proteus vulgaris*) following ureterosigmoidostomy and 2 of appendiceal peritonitis. They noted that the strikingly rapid improvement suggested that the toxin-producing activity of the bacteria was being swiftly brought under control. Long and his colleagues⁸³ obtained dramatic response in 2 cases of peritonitis and in 2 cases of localized postoperative infections, 1 a fecal fistula, the other a purulent sinus following drainage of a pelvic abscess

While chemotherapy cannot substitute for surgery, it has been suggested⁸⁷ that if for any reason the patient cannot be treated surgically, a combination of aureomycin and penicillin should give excellent results.

INFECTIONS OF THE MOUTH—Distelheim and Sulzberger²⁰³ obtained striking response to aureomycin applied locally in a case of aphthous stomatitis. The etiology was unclear, but was thought to be either viral or mixed. The mouth was rinsed with freshly prepared 0.5 per cent aqueous solution of aureomycin, 4 times daily. The painful recurrent ulceration and necrosis, which had for 5 years resisted treatment, began to heal almost at once. Pain and burning were gone by the second day of aureomycin therapy and on the sixteenth day only outlines remained to mark the site of healed lesions.

A series of 25 cases of infection of the oral cavity treated with oral aureomycin, has been described by Jacobs and Jacobs.²⁰² Bacteriologic studies were not done, but the series is included at this point in view of the mixed bacterial flora usually found in such cases. The conditions treated were: acute periostitis,¹ acute subperiosteal abscess,¹ acute herpetic stomatitis and gingivitis,² acute suppurative gingivitis,¹ acute submaxillary adenitis,³ cellulitis,² alveolar abscess,² diffuse osteomyelitis of the mandible,¹ acute circumscribed osteomyelitis,¹ acute parodontal abscess,¹ subacute infected lymph node,¹ acute osteitis,¹ acute pericoronal abscess,² subacute pericoronitis.¹⁶ In 4 cases, penicillin had been given without success and the subperiosteal abscess had also been incised and drained. Surgical intervention was, of course, practiced when indicated (8 cases in all). Results were excellent in 16 cases, good in 6, fair in 2. Another patient was improving.

ULCERATIVE COLITIS—Although the primary etiologic

agent is unknown, secondary infection develops in the damaged mucosa and contributes greatly to the damage caused by this disease

Wright and Schreiber⁵¹ describe aureomycin as the best known remedy for ulcerative colitis, producing prompt improvement and weight gain, with definite relief of pain and bleeding and reduction in the number of bowel movements Glass²⁰⁴ noted improvement in 1 case and draws attention to certain physical and psychological evidences of B complex deficiency during aureomycin therapy

Wright and Strax,²⁰⁵ a little more than a year ago, observed a case of pyoderma gangrenosa treated with aureomycin and found its effect on an associated colitis so impressive that they proceeded to apply it in other cases Chronic debilitating infections are not infrequently accompanied by suppurative and ulcerative skin lesions of mixed character In the first case treated by these workers, severe and extensive gangrenous pyoderma complicated an intractable ulcerative colitis of 17 years' duration It was felt that the patient's life depended upon operation, which she was too ill to undergo safely Aureomycin not only produced dramatic cure of the surface lesions but so improved the bowel condition and the general health, that it was possible to perform a subtotal colectomy and to restore her to normal activity and well-being.

Since that time, they have given aureomycin to 13 active (with diarrhea) and 2 quiescent cases of ulcerative colitis²⁰⁶ with most encouraging results All of the former group evidenced improvement in bowel function and general health The reduction in the number of stools was at

least 50 per cent in 11 cases. Twelve patients also developed improved consistency of the stools. Treatment was continued until a considerable time after maximum improvement had taken place, which might not be for 4 or 5 weeks.

The 2 quiescent cases showed less marked benefit, but both improved physically and functionally. The authors consider aureomycin to be superior to any drug previously used in the treatment of idiopathic ulcerative colitis and have discontinued the use of sulfonamides for this condition.

Strax and Wright⁷⁷ also noted beneficial effects on the diarrhea of two patients following ileotransverse colostomy for ileitis, and relief of severe pain in 2 cases of postcholecystectomy syndrome.

SKIN INFECTIONS—Because aureomycin appears to have little or no allergic effect, Hollander and Hardy⁴⁷ were led to study its action when used locally in ointment form, in a diversified series of 136 cases of skin disorders and as a surgical dressing after office surgical procedures. A number of these patients had undergone lengthy therapy before being put on aureomycin.

The 79 cases of skin infections included both infectious and atopic dermatoses. In this group, results were excellent in 60 and sensitivity reactions occurred in 10, usually in those cases whose response was listed as unsatisfactory and in whom there was other evidence of an allergic diathesis. Results were uniformly excellent in all of the 57 patients for whom aureomycin was used as a postoperative dressing for various conditions, including excision of

carcinomata or of infected cysts. There were no sensitivity reactions in this group, a further indication of the lack in aureomycin of significant allergenic properties or irritating action on normal skin. In at least 1 of the surgical patients, penicillin had caused the development of sensitivity.

The authors have drawn particular attention to the satisfactory response of 1 patient with pustular psoriasis. This condition has always been completely unresponsive to any form of treatment hitherto applied.

URINARY INFECTIONS—The genitourinary tract is unique in the therapeutic problems presented by infection of any of its component parts. The narrowness of its tubular passages makes it easy for obstruction to be produced by scarring, foreign bodies, swelling of neighboring structures, congenital malformations, etc. Acute infections of a normal urinary system are as easy to combat as those elsewhere in the body, but in the presence of obstruction and urinary stagnation, such infections have a tendency to become chronic. Not only does chronicity develop, but secondary invasion is extremely common. In some cases, these complicating infections may reach the genitourinary tract through the blood stream or by upward extension from without, but the close proximity of the gastrointestinal canal makes the coli-aerogenes group and other intestinal bacteria by far the most frequent invaders.

Before aureomycin, the usual treatment of chronic or mixed infections was by means of a variety of agents, either successively or in combination, but the results were

far from satisfactory, even after the relief of any obstructive or other contributory cause, and the establishment of free drainage. The effectiveness of aureomycin against most of the common infecting organisms, its high urinary concentration, and the lack of development of drug resistance, now permit the successful use of a single drug. Two organisms, *Proteus vulgaris* and *Pseudomonas aeruginosa*, are very resistant and may persist or appear for the first time during aureomycin therapy.³⁴

It would seem that the incidence and pathogenicity of *Aerobacter aerogenes* in the genitourinary tract has recently increased. It has proved relatively insensitive to the usual therapeutic agents, but Wilhelm and his associates²⁰⁷ have found that aureomycin has proved the most consistently efficacious of these. They have used aureomycin in a series of 23 cases of persistent *Aerobacter aerogenes* infection of the urinary tract, with excellent immediate clinical response in 21 cases. The results were often very remarkable. Patients with chronic severe pyuria frequently void clear urine within 24 to 48 hours, in spite of the presence of residual urine. There was noted a tendency to recurrence, the urine, however, becoming sterile again after an additional course of aureomycin.

Cases resistant to the sulfonamides, penicillin or streptomycin, whether alone or in combination, have been found to respond to aureomycin.^{33 208-210} Rutenburg and Schweinburg²¹¹ treated an unselected group of urinary infections with aureomycin. Most of these had been resistant to other forms of treatment and 20 of the 26 showed obstructive urinary conditions. In all cases the

clinical symptoms disappeared very rapidly, usually within 24 to 48 hours, regardless of whether the urine had or had not become sterile. Permanent sterilization was obtained in 16 cases. Where infection persisted, clinical signs and symptoms were apt to return after stopping treatment. They noted a close relationship between the clinical response of an organism and its *in vitro* sensitivity to aureomycin. In every case aureomycin was successful in eliminating from the urine *Aerobacter aerogenes*, *Escherichia coli*, *Proteus vulgaris*, *Staphylococcus aureus hemolyticus* and *Streptococcus faecalis*. Five out of 11 strains of *Pseudomonas aeruginosa* were sensitive to aureomycin and were cleared from the urine. In simple infections, there were 5 failures. One was due to *Escherichia coli* and 4 to *Pseudomonas aeruginosa*, the bacteria being resistant to aureomycin *in vitro* as well.

Brainerd and co-workers⁴⁶ gave aureomycin to 14 patients who had previously been treated unsuccessfully with other chemotherapeutic agents. In 3 acutely infected cases rapid disappearance of symptoms and sterilization of the urine resulted. The other 11 cases were chronic ones associated with urinary obstruction, and although the urine could be temporarily sterilized in 10 of them, relapse or reinfection occurred in all cases that were followed up. However, aureomycin seemed to be able to control the infection in 1 case of hydronephrosis of pregnancy so that the fetus could be carried to term, and in 1 case of obstructive infection so that pyelolithotomy could be carried out. *Pseudomonas aeruginosa* was again found to be the most difficult infection to treat successfully.

Strax and Wright⁷⁷ consider aureomycin to be the drug of choice in all serious urinary infections. A group of 16 adults, most of them in the older age groups, was selected by Collins and Finland²¹² for treatment with aureomycin. All except one of these were chronic infections which had failed to respond to treatment. The acute case had previously been untreated and was one of acute pyelonephritis complicating pregnancy. Ambulatory treatment was used in 12 of these patients. In almost all of them there was a long history of severe complicating factors and chronic obstruction. Symptomatic relief and bacteriologic cure followed the use of aureomycin in the acute pyelonephritis of pregnancy. While symptomatic and bacteriologic results were good in most of the other patients, improvement could not be maintained, owing to the continued presence of urinary stagnation.

An extremely obstinate case of urinary infection has been reported by Abrams and co-workers²¹³ in a patient with hyperparathyroidism and nephrolithiasis. Within 24 hours of starting aureomycin therapy the urine from the right kidney and bladder was sterile, but a heavy growth of *Pseudomonas aeruginosa* was obtained from the left nephrostomy tube. Two weeks later *Pseudomonas aeruginosa* and *Escherichia coli* were found in the urine from both kidneys and the bladder. Nephrectomy was done and within 24 hours aureomycin had sterilized the urine. The patient was afebrile within 3 days. Eight months later the urine was still sterile on culture. Carroll and co-workers²¹⁴ have noted unusually favorable results from the use of aureomycin following transurethral surgery. Treated patients

had clear urine within a week, in 9 out of 10 cases, while without aureomycin persistent pyuria is a very frequent occurrence

Harvey, Mirick and Schaub⁴¹ have reported uniformly satisfactory results in 15 patients, 14 of whom had not responded to other types of chemotherapy. The only failure was a case of *Pseudomonas aeruginosa* infection. They avoid catheterization, believing that it increases the likelihood of stubborn secondary infection by *Proteus vulgaris*.

INDICATIONS FOR AUREOMYCIN

In the preceding pages, a representative selection of published literature has been given. With a drug of such newness as aureomycin it is obviously impossible to achieve universal acceptance of every claim for its usefulness as expressed in each publication. Accordingly, there are certain generally accepted claims which represent the present irreducible minimum of the usefulness of aureomycin. Additions to this list are certain to be made at frequent intervals. The following indications are now well accepted—

African tick-bite fever, acute amebiasis, bacterial and virus-like infections of the eye, bacteroides septicemia, boutonneuse fever, acute brucellosis, Gram-positive infections (including those caused by streptococci, staphylococci, and pneumococci), Gram-negative infections (including those caused by the coli-aerogenes group), gran-

uloma inguinale, *H. influenzae* infections, lymphogranuloma venereum, penicillin-resistant gonorrhea, peritonitis, primary atypical pneumonia, psittacosis (parrot fever), Q fever, rickettsialpox, Rocky Mountain spotted fever, subacute bacterial endocarditis resistant to penicillin, tularemia and typhus

ADMINISTRATION AND DOSAGE

Oral Dosage

Accepted dosage is 25 mg per kilo of body weight every 24 hours, divided into 4 equal doses, or 500 mg every 6 hours for average adults. Full dosage should be continued for 1 to 2 days beyond the time when the temperature has become normal. In infections which do not respond satisfactorily within 48 hours, the dosage should be increased to 500 mg. or more every 3 hours. Similarly, in severe infections, such as bacterial endocarditis, Q fever, or infections resistant to other chemotherapy, the initial dosage should be increased, or preferably, the sensitivity of the organisms should be determined, and dosage prescribed accordingly.

The optimum treatment schedule for brucellosis with aureomycin has not been determined fully. The preliminary administration of 250 mg to 500 mg daily for 2 to 3 days, followed by progressively increased amounts of aureomycin up to the full calculated therapeutic dosage, may be desirable in chronic cases, by reducing the likelihood of gastrointestinal disturbances together with skin

and mucous membrane lesions, such as have been reported at times as being associated with the therapy of chronic brucellosis

For infections of the oral cavity, the ordinary capsule form of administration may be employed or aureomycin troches may be placed in the mouth. By retaining these until they have dissolved in the saliva, high local concentrations may be ensured. One or 2 should be taken every 2 or 3 hours depending on the severity of the infection.

Parenteral Dosage

Intravenous therapy should be employed only in emergency for hospitalized patients who are moribund *Because of the possibility of thrombophlebitis at the site of injection, intravenous therapy should be discontinued as soon as the patient can take aureomycin orally* Aureomycin should be given intravenously in a dosage of 500 mg twice daily This dosage may be adjusted upward, to as much as 500 mg every 6 hours, *never more*, or downward according to the severity of the infection. Not less than 10 cc of diluent should be employed for each 100 mg of aureomycin Solutions should be prepared immediately before use Approximately 5 minutes should be required for injecting each 10 cc. dose.

Ophthalmic Dosage

In ocular infections, aureomycin may be applied locally in the form of a 0.5 per cent solution of aureomycin borate, 1 or 2 drops being placed in both eyes every 2 hours, or oftener, according to the severity of the infection Systemic therapy may also be used simultaneously.

Precautions

Aureomycin is relatively nontoxic. Side reactions have been reported consisting of nausea, vomiting or looseness of stools, but these reactions have steadily decreased with increasing purification of material, so that it is believed that they are not of any importance at the present time. If annoying symptoms should occur during oral administration, they can usually be controlled by giving half the dosage every 3 hours, instead of every 6 hours, or by giving half the dosage at 6-hour intervals for 1 or 2 doses. Allergy to aureomycin may occur, but would appear to be rare. Since oral aureomycin affects the normal growth of bacteria in the intestine, it is advisable to replace factors of the B Complex supplied by these bacteria with an oral B Complex supplement, in all patients receiving aureomycin by mouth for periods longer than 7 days.

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